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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/604,727	08/13/2003	Itzhak Bentwich	050992.0200.06USCN	1726

37808 7590 07/02/2008

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EXAMINER	
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ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/02/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/604,727	BENTWICH, ITZHAK	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10-6-06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

CFR §1.821(d) reads as follows:

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

In the instant case, at least paragraph 0123 of the specification as well as Figures 21A, 22A, and 23A contain nucleic acid sequences which are not preceded by "SEQ ID NO:". Applicant is encouraged to carefully review the entire application and ensure sequence rule compliance as set forth in CFR §1.821(d).

Status of Claims

In the instant case, claims 1-16 are currently pending and under examination on the merits.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 35 U.S.C. 120 as follows:

This application is claiming the benefit of prior-filed nonprovisional application No. 10/293,338 under 35 U.S.C. 120. Note that 10/293,338 was abandoned on April 14, 2003 and the instant application was filed on August 13, 2003. Copendency between the current application and the prior application is required. Since the applications are not copending, the benefit claim to the prior-filed nonprovisional application is improper. Applicant is required to delete the reference to the prior-filed application from the first sentence(s) of the specification, or the application data sheet, depending on where the reference was originally submitted, unless applicant can establish copendency between the applications.

Accordingly, the benefit of an earlier filing date of application No. 10/293,338 is denied and therefore the instant filing date of August 13, 2003 will be the effective filing date for claims 1-16.

Specification

The disclosure is objected to because of the following informalities:

1) The disclosure contains sequence rule non-compliant subject matter. See page 2 of this Office action and the attached Notice to Comply.

2) The abstract as well as the title of the instant application contain the term, "novel". Note that the abstract and the title of a patent application should be descriptive of the claimed subject matter, which is presumed to be novel. See M.P.E.P. §606. Accordingly, the term "novel" is not descriptive of the claimed subject matter in the instant case because it is obvious that claimed invention be novel.

3) The specification does not provide brief description of drawings for Figures 18, 19, and 20.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to bioinformatically detectable novel genes wherein the first half of an RNA precursor is a "partial inversed-reversed" sequence of a second half thereof. The term "partial inversed-reversed" is neither defined in the claims nor described in the specification. Further, the term is not an art-recognized term, wherein one of ordinary skill in the art can readily recognize the structure of the RNA precursor claimed in the instant case. That is, one of ordinary skill in the art cannot ascertain the metes and bounds encompassed by the term "partial inversed-reversed", nor can the artisan envision the precise structure of the novel genes claimed

in the instant case. For examination purpose, the term will be interpreted as "partial complementary" in light of the nature of the claimed subject matter and the content of the specification, which teaches that the claimed bioinformatically detectable novel genes and the RNA precursors pertain to microRNA sequences.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-12 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* methods of inhibiting target gene in a cell or *in vivo* methods of inhibiting target gene in a non-mammalian organism, does not reasonably provide enablement for *in vivo* methods of inhibiting target gene in a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized *In re Wands*, 858 F.2d 731,737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'." (Wands, 8 USPQ2d 1404). There are many factors to be considered when determining whether there is sufficient

evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of claims 11-12 and 15 encompasses both *in vitro* and *in vivo* embodiments. As of the earliest filing date granted in the instant case, that is August 13, 2003, the state of the art and the level of one of ordinary skill in the art pertaining to inhibiting target gene expression in a living mammalian organism via an miRNA molecule were far from being highly advanced, as evidenced by the lack of prior art of record filed in the IDS that teaches miRNA/RNAi-mediated *in vivo* inhibition of target gene in a mammal. Further, the unpredictability of delivering miRNAs into target cells with requisite RNAi-inhibitory effects still remained prominent in the art even many years after the date of the instant invention. See for example Schmidt (*Nature Biotechnology,* March 2007, 25:273-275). As Schmidt discusses several RNAi patents (see page 273), he points out that "Though RNAi has become invaluable for basic research, its therapeutic potential is unknown. Delivering RNAi drugs to target cells poses difficult challenges; largely because of this, drug-development with RNAi remains mainly in preclinical stages." (emphasis added). In the article, Schmidt also teaches that "It can be notoriously difficult for oligonucleotides to penetrate cell membranes, and evade immune system attacks. Without solving the delivery problem, drug makers will be unable to deliver on RNAi's therapeutic promise." See page 275. Hence, the unpredictability of suppressing gene expression

via siRNAs in a mammal *in vivo* with corresponding inhibitory effects was widely recognized in the art as of the earliest filing date granted in the instant application.

Moreover, the instant specification is completely silent with regard any inhibitory methods, either *in vitro* or *in vivo,* as it provides no working example comprising all the limitations set forth in the claims. The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. See *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004): "Nascent technology, however, must be enabled with a specific and useful teaching. The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." See also MPEP §2164.03. (emphasis added)

In view of the totality of the factors listed above and the reasons stated above, it is concluded that one of ordinary skill in the art would not have been able to practice the entire scope of the claimed invention without undue experimentation at the time of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Grad et al. (*Molecular Cell,* 2003, 11:1253-1263).

The claims are drawn to bioinformatically detectable miRNAs of about 18-24 nucleotides in length, whose function is bioinformatically deducible and said function is to modulate target gene expression or cell type of a daughter cell, probes for detecting the miRNAs, and methods of inhibiting at least one target gene in a cell *in vitro* by introducing a probe comprising the bioinformatially detectable miRNAs that utilize RNAi pathway.

Grad et al. teach that miRNAs of about 22 nucleotides and their target genes are computationally predicted and experimentally verified. They teach that miRNAs bind their target mRNAs in the 3' or 5' UTR region of the target mRNAs and regulate the expression/activity of target mRNAs at the translational level via the RNAi mechanism. They teach that miRNAs play tissue-specific regulatory functions at various developmental stages as evidenced by Northern blot, PCR detection, and phenotype analyses. Accordingly, all claim limitations are taught by Grad et al.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Rhoades et al. (*Cell,* 2002, 110:513-520, applicant's citation).

The claims are described above.

Rhoades et al. teach that miRNAs are identified based on bioinformatics and their target mRNAs can be identified by computational algorithms. They teach that the predicted miRNA target mRNAs are involved in various biological regulatory functions such as development, cell division and differentiation, and cell fate decisions. They teach that miRNAs bind their target mRNAs and mediate the cleavage of target mRNAs via RNAi mechanism. See the entire reference. Accordingly, all claim limitations are taught by Rhoades et al.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 102(a) as being anticipated by Lai et al. (*Genome Biology,* 2003, 4:R42).

The claims are described above.

Lai et al. teach that miRNAs of 21-22 nucleotides are computationally detectable and identifiable by using a computational program "MiRseeker". They teach that miRNAs are posttranscriptional regulators of target gene expression by functioning in the RNAi pathway. They also teach that target mRNAs for some miRNAs have already been identified in the art. They teach that the computationally detectable miRNAs are experimentally verified for their functions and expression profiles. They teach that miRNA expression is detected by Northern blot analysis using miRNA probes and that expression of most miRNAs are highly tissue-specific and time-specific and that some miRNAs are regulators of developmental timing and expression. See the entire reference. Accordingly, all claim limitations are taught by Lai et al.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al. (*Science,* 2001, 294:862-864, applicant's citation).

The claims are described above.

Lee et al. teach that that miRNAs of about 22 nucleotides are identified by using informatics and molecular cloning methods. They teach that miRNAs perform various functions including regulating gene expression and development as they are expressed in a tissue-specific, developmental timing-specific manner as evidenced by Northern blot analysis. See the entire reference. Accordingly, all claim limitations are taught by Lee et al.

Claims 1-9 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Lagos-Quintana et al. (*Science,* 2001, 294:853-858, applicant's citation).

The claims are described above.

Lagos-Quintana et al. teach that the nucleotide sequences, functions, and the potential targets of miRNAs can be identified by using bioinformatics. They teach that miRNAs are generally 20-23 nucleotides in length and function as posttranscriptional regulators of gene expression. They teach that one of skill in the art can identify temporal and spatial (tissue-specific) expression patterns of miRNAs utilizing various molecular and genetics tools such as Northern blot analysis comprising detecting miRNAs by using probes. They teach that some miRNAs are responsible for determining cell fate for daughter cells (e.g., maternal contribution from germ cells or tissue-specificity) and therefore miRNAs may be used in methods to "direct

the regulation of specific gene targets and may also lead to new ways of reprogramming tissues". See pages 853-854 and 857.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lagos-Quintana et al. (*Science,* 2001, 294:853-858, applicant's citation) in view of Cullen et al. (US 2004/0053411 A1).

The claims are drawn to bioinformatically detectable miRNAs and vectors comprising the miRNAs and methods of inhibiting target genes of the miRNAs via RNAi pathway by introducing the vectors into cells *in vitro*.

Lagos-Quintana et al. teach that the nucleotide sequences, functions, and the potential targets of miRNAs can be identified by using bioinformatics. They teach that miRNAs are generally 20-23 nucleotides in length and function as posttranscriptional regulators of gene expression. They teach that one of skill in the art can identify temporal and spatial (tissue-specific) expression patterns of miRNAs utilizing various molecular and genetics tools such as Northern blot analysis comprising detecting miRNAs by using probes. They teach that some miRNAs are responsible for determining cell fate for daughter cells (e.g., maternal contribution

from germ cells or tissue-specificity) and therefore miRNAs may be used in methods to "direct the regulation of specific gene targets and may also lead to new ways of reprogramming tissues". See pages 853-854 and 857. Lagos-Quintana et al. do not teach that miRNAs modulate target gene expression via RNAi pathway by transfecting a vector comprising a miRNA into cells.

Cullen et al. teach that miRNAs inhibit target genes via RNAi mechanism by introducing an expression vector comprising a miRNA sequence. See paragraphs 0006, 0055-0056; claims 1-27.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make an expression vector comprising bioinformatically identified miRNAs of Lagos-Quintana et al. and use it to inhibit target gene expression in cells as taught by Cullen et al.

One of ordinary skill in the art would have been motivated to do so because making an expression vector comprising a miRNA and using it to inhibit target gene expression via RNAi mechanism in a cell *in vitro* were known in the art at the time of the invention as taught by Cullen et al. Hence, the skilled artisan who had identified miRNAs via bioinformatics and genetics tools as taught by Lagos-Quintana et al. would have had a reasonable expectation of success in making an expression vector comprising the newly identified miRNAs and use it for RNAi-mediated target gene inhibition in cells *in vitro*. Accordingly, the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-16 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-16 of copending Application No. 10/535,164. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

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